



EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Statement on the safety of 'Cetyl Myristoleate Complex' as an ingredient in food supplements

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SCIENTIFIC OPINION

Statement on the safety of ‘Cetyl Myristoleate Complex’ as an ingredient in food supplements¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to update its opinion on the safety of ‘Cetyl Myristoleate Complex’ (CMC) as a novel food ingredient in the light of additional information submitted by the applicant. In its previous opinion of 2010, the Panel concluded that the safety of CMC as an ingredient in food supplements at an intake of 3.3 g per day has not been established. This conclusion was based on the considerations that in the absence of appropriate data on absorption, distribution, metabolism and excretion, the provided toxicological data were insufficient. In 2012, the Commission requested EFSA to review and update its opinion by taking into account a new subchronic 90-day oral toxicity study conducted with “Cetylated Fatty Acid Esters Powder 50 %” in mice. In its opinion of 2013, the Panel considered that a new 90-day study cannot serve as a reliable source of information supporting the absence of adverse effects of CMC. The dossier of this new mandate contains three new references which were not submitted and hence not considered in the previous assessments. The Panel notes that two references do not address the concerns expressed by the Panel in its previous assessments. The third reference provided is a report on an *in vitro* hydrolysis study demonstrating a low rate of hydrolysis of cetyl myristoleate and cetyl myristate. The Panel notes the low rate of hydrolysis of the two esters found in this *in vitro* hydrolysis study and therefore reiterates the need for adequate safety information on the unhydrolysed esters contained in CMC as expressed in its opinions of 2010 and 2013. The Panel concludes that, even after considering the newly submitted information, the safety of ‘Cetyl Myristoleate Complex’ has not been established.

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KEY WORDS

Cetyl Myristoleate Complex, CMC, cetyl myristoleate, cetyl myristate, cetylated fatty acid, ingredient, novel food

¹ On request from the European Commission, Question No EFSA-Q-2014-00166, adopted on 25 June 2014.

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SUMMARY

'Cetyl Myristoleate Complex' (CMC) consists of 50 % cetylated fatty acids (CFAs), 48 % corn starch and 2 % silicon dioxide. The applicant proposed a daily intake of 3.3 g CMC (1.65 g CFAs) which contains approximately 660 mg of both cetyl myristoleate and cetyl myristate, the two main compounds of CMC.

In 2009, the European Commission asked EFSA to carry out an assessment of the safety of 'Cetyl Myristoleate Complex (CMC)' with an intended daily intake of 3.3 g per person per day in the context of Regulation (EC) No 258/97. In 2010, the Panel on Dietetic Products, Nutrition and Allergies (NDA) concluded that, based on the available data, the safety of CMC has not been established (EFSA NDA Panel, 2010). This conclusion was based on the considerations that, in the absence of appropriate data on absorption, distribution, metabolism and excretion, the provided toxicological data were insufficient.

In 2012, the Commission requested EFSA to review and update its opinion by taking into account a report of a new subchronic 90-day oral toxicity study conducted with "Cetylated Fatty Acid Esters Powder 50 %" (Cetyl Myristoleate Complex, CMC) in mice (CMC Study Report, 2012). In 2013, the NDA Panel noted that the new 90-day study and its report have many shortcomings, and considered that this study cannot serve as a reliable source of information supporting the absence of adverse effects of CMC (EFSA, 2013). The Panel also noted that apart from information on the safety of the hydrolysis moieties, and in the absence of sufficient data with respect to kinetics of hydrolysis, adequate safety information on the parent compounds of CMC remains relevant. The Panel reiterated its previous conclusion from 2010 that the safety of 'Cetyl Myristoleate Complex' has not been established.

Following a request from the European Commission, the NDA Panel was asked in 2014 to update its opinion on the safety of 'Cetyl Myristoleate Complex' (CMC) with an intended daily intake of 3.3 g per person as a novel food ingredient in food supplements in the light of additional information provided by the applicant.

The dossier of this new mandate contains three new references which were not submitted and hence not considered in the previous assessments. The Panel notes that two references do not address the concerns expressed by the Panel in its previous assessments, i.e. the absence of sufficient data with respect to kinetics of hydrolysis, the limitations and shortcomings of the toxicological data for CMC, and the safety of the parent compounds, i.e. cetylated fatty acids, mainly cetyl myristoleate and cetyl myristate.

The third reference is a study report on an *in vitro* hydrolysis study demonstrating that cetyl myristoleate and cetyl myristate are to a large extent resistant to hydrolysis in simulated digestive fluids. The Panel notes the low rate of hydrolysis of the two esters found in a newly provided *in vitro* hydrolysis study and therefore reiterates the need for adequate safety information on the unhydrolysed esters contained in CMC as expressed in its opinions of 2010 and 2013.

The Panel concludes that, even after considering the newly submitted information, the safety of 'Cetyl Myristoleate Complex' has not been established.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

On 9 July 2010, EFSA adopted a Scientific Opinion on the safety of 'Cetyl Myristoleate Complex' as a novel food ingredient (EFSA, 2010). The conclusion of the EFSA Opinion was that the safety of Cetyl Myristoleate Complex has not been established.

On 12 June 2012, the Commission requested EFSA to review this Opinion based on the new information provided by the applicant. On 31 May 2013, EFSA adopted a statement reiterating its view that the safety of the product could not be established.

The applicant has now provided additional information on the product.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002, the European Commission asks the EFSA to revise and update its scientific Opinion on Cetyl Myristoleate Complex in light of the additionally submitted information.

ASSESSMENT

1. Introduction

In 2009, the European Commission asked EFSA to carry out an assessment of the safety of 'Cetyl Myristoleate Complex (CMC)' with an intended daily intake of 3.3 g per person from food supplements in the context of Regulation (EC) No 258/97. In 2010, the Panel concluded that, based on the available data, the safety of CMC has not been established (EFSA NDA Panel, 2010).

This conclusion was based on the considerations that (i) a provided rat study on the absorption and distribution of ^{14}C -labelled cetylated fatty acids (CFAs) had limitations in the design and the test substance used with respect to the proposed novel food ingredient, (ii) no information was provided on the extent of intestinal hydrolysis of the CFAs after oral intake, (iii) limited information was provided on the distribution of absorbed unhydrolysed CFAs and (iv) no information was provided on the metabolism and excretion of such intact CFAs. In the absence of appropriate data on absorption, distribution, metabolism and excretion (ADME), the provided toxicological data were considered insufficient. No subchronic oral toxicity study and no chronic toxicity study conducted with cetyl myristoleate or CMC had been provided in the original dossier.

In 2012, the Commission requested EFSA to review and update its 2010 opinion by taking in account a report of a new subchronic 90-day oral toxicity study conducted with "Cetylated Fatty Acid Esters Powder 50 %" (Cetyl Myristoleate Complex, CMC) in mice (CMC Study Report, 2012). In 2013, the Panel noted that the new 90-day study and its report have many shortcomings and considered that this study cannot serve as a reliable source of information supporting the absence of adverse effects of CMC (EFSA, 2013). The Panel also noted that apart from information on the safety of the hydrolysis moieties, and in the absence of sufficient data with respect to kinetics of hydrolysis, adequate safety information on the parent compounds of CMC remained relevant. The Panel reiterated its conclusion from 2010 that the safety of 'Cetyl Myristoleate Complex' has not been established.

'Cetyl Myristoleate Complex' consists of 50 % cetylated fatty acids, 48 % corn starch and 2 % silicon dioxide. The applicant proposed a daily intake of 3.3 g CMC (1.65 g CFAs), which contains approximately 660 mg of both cetyl myristoleate and cetyl myristate, the two main compounds of CMC.

2. Additional information provided

The dossier of this new mandate contains three new references which were not submitted and hence not considered in the two previous opinions.

One study provides analytical data on the fatty acid composition of human adipose tissue (Insull and Bartsch, 1967). This article reports that myristic and myristoleic acid occur naturally in human adipose tissue at proportions of about 2.5–3 % and 0.5–0.7 % of its fatty acids.

One review (CIR, 1988) provides an overview on toxicological studies with cetyl alcohol, which included studies on inhalation toxicity, acute and subchronic dermal toxicity, skin irritation, mucous membrane irritation, ocular irritation, acute oral toxicity and mutagenicity. This review also summarised human studies on skin irritation and sensitisation and photosensitisation.

The Panel notes that these two studies do not address the concerns expressed by the Panel in its previous assessments, i.e. the absence of sufficient data with respect to kinetics of hydrolysis, the limitations and shortcomings of the toxicological data for CMC and the safety of the parent compounds, the CFAs, mainly cetyl myristoleate and cetyl myristate.

The third reference provided is an unpublished report on an *in vitro* hydrolysis study (Redaelli, 2010). This study investigated the stability of the two main constituents of CMC, cetyl myristoleate and cetyl myristate, in the presence of physiological fluid simulants such as saliva, gastric and intestinal juice

simulants at body temperature. Gas chromatography was used to quantify the content of the anticipated hydrolysis products: myristic acid, myristoleic acid and cetyl alcohol.

The study reported that cetyl myristoleate and cetyl myristate are to a large extent resistant to hydrolysis in the simulated digestive fluids. When treated with saliva and gastric fluid simulants, after four hours the maximum hydrolysis rates for both compounds were $\leq 5\%$; when treated with the intestinal fluid simulant, after four hours the maximum hydrolysis was about 8 %.

The applicant also claims a "history of safe use" of CMC and states that EHP Products Inc., the manufacturer of CMC, and its affiliates have produced and sold over 95 000 kg CMC for animal and human use (compared with 10 000 kg up to 2008, as stated in the dossier considered by EFSA for its opinion of 2010). The Panel considers that sales figures do not address safety concerns.

DISCUSSION

The Panel notes the low rate of hydrolysis of the two esters found in a newly provided *in vitro* hydrolysis study and therefore reiterates the need for adequate safety information on the unhydrolysed esters contained in CMC as expressed in its opinions of 2010 and 2013 (EFSA NDA Panel, 2010, 2013).

CONCLUSION

The Panel concludes that also after considering the newly submitted information, the safety of 'Cetyl Myristoleate Complex' has not been established.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier "Cis-9-Cetyl Myristoleate. History of its safety of use. With related documents and studies; 8 November 2013".
2. Letter from the European Commission to the European Food Safety Authority with the request to review the Opinion on the safety of 'Cetyl myristoleate complex' as a novel food ingredient in food supplements. Ref. Ares(2014)589079—05/03/2014, received on 6 March 2014.

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- Insull W Jr and Bartsch GE, 1967. Fatty acid composition of human adipose tissue related to age, sex, and race. American Journal of Clinical Nutrition, 20, 13–23.
- Redaelli, 2010. Investigation of cetylmyristoleate complex behaviour toward physiological fluid stimulants. 30/09/2010, Choris, Doc. No 73–10.

ABBREVIATIONS

ADME	absorption, distribution, metabolism and excretion
CFA(s)	cetylated fatty acid(s)
CMC	Cetyl Myristoleate Complex